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metabolism products, particularly tetracosapentaenoic acid (24:5n-3) and tetracosahexaenoic acid (24:6n-3), were increased in atrial, but not in ventricular myocardium after intrapericardial HUFA administration, which was associated with a higher ventricular potential to finalize DHA synthesis. Tetracosahexaenoic acid requires carnitine octanoyltransferase, a family member of carnitine acetyltransferases, for transportation into the endoplasmic reticulum to undergo final beta-oxidation. It was previously shown that carnitine palmitoyltransferase (1b and 2) is reduced in atrial compared with ventricular myocardium. It is proposed to evaluate beta-oxidation as a novel target for endogenous HUFA concentrations. In accordance with the report by Nigam et al. (1), no changes of HUFA levels were found after a challenge with the proinflammatory peroxisome proliferator-activated receptor-alpha agonist fenofibrate or in a talcum-induced pericarditis model.

Up to now, involvement of cardiac load conditions and the differential endogenous HUFA metabolism were not sufficiently taken into account, which may provide a rationale for divergent findings of HUFA treatment in previous trials.

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Please note: In memory of Heinz Rupp. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Applying Cluster Analysis to Data of Previously Published Chronic Heart Failure Trials

I enjoyed studying the contribution by Ahmad et al. (1), and the accompanying editorial by Francis et al. (2), published in the October 28, 2014 issue of the *Journal*, about the application of cluster analysis to the data from 1,619 participants of HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study. The investigators reported that cluster analysis provided an advantage over traditional phenotyping, based on the subjective symptomatic assessment of the patients via the New York Heart Association functional classification I to IV, and A to D stages, and imaging-based left ventricular ejection fraction (LVEF) in predicting outcomes (all-cause and cardiovascular, mortality, and hospitalization risks) and response to surrogate parameters (change in peak oxygen consumption and in standard 6-min walk test). Clinicians following longitudinally large numbers of heart failure (HF) patients with a reduced LVEF in cardiology clinics have long been accustomed to the incongruity between the functional classification/staging (New York Heart Association class II to IV) and LVEF (≤35%) and outcomes of their patients, stemming from our current coarse phenotyping of a highly heterogeneous disease as HF and the impact of comorbidities.

Ahmad et al. (1) arbitrarily employed 45 prespecified clinical variables and identified 4 phenotypic clusters, with intracluster similarities and intercluster differences, in which they showed diverse mortality and hospitalization rates. It is of interest that in the exhaustive list of variables used (1), a measure of the patients' overall compliance with their management in general, and with drug taking in particular, is missing (issues of frequent concern in cardiology clinics), for which the investigators are not responsible. Ahmed et al. (1) and Francis et al. (2) cited the reasons why a number of trials (refs. 7, 8, and 35 in Ahmed et al. [1]) and patients with HF with a reduced LVEF (refs. 5 to 8 in Francis et al. [2]) "have failed to meet their endpoints" (2), and Ahmed et al. (1) stated that "we have seen such little progress in developing new treatments for this disorder."

Although we need to adopt the philosophy of enhanced and refined phenotyping in designing future HF clinical trials (2), what should have

precedence now are the following objectives: 1) a "culture" change in practice and research, conducive to distancing ourselves from the attachment and the "false security" provided by the New York Heart Association functional classification I to IV, A to D staging and LVEF, when phenotyping our HF patients, and adopting more liberal classification schemes; and 2) application in research of cluster analysis to existing data from previously published randomized HF clinical trials, and data from electronic medical records, modeled after the present study (1), in an attempt to come up with winning sets of a few clusters that will outperform our current HF classification systems. These 2 objectives will pave the way to a future when design of "rational" clinical trials (2) will be feasible and cost-effective.

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Systems Biology and Clinical Phenotypes of Heart Failure Syndrome

The paper by Ahmad et al. (1) used cluster analysis to describe clinical phenotypes in chronic heart failure (HF) and identified 4 "phenotypically distinct and clinically meaningful groups." Their cluster analysis was based on 45 clinical variables and therapeutic effects from 1,619 patients of the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study (2), which evaluated the effect of exercise training on morbidity and mortality in patients with chronic systolic HF. Ahmad et al. (1) named the patient clusters "chronic heart failure phenotypes" and emphasized "the high degree of disease heterogeneity" and the necessity for more precise phenotyping of the HF syndrome.

In our opinion, the cluster analysis of 45 variables and their grouping in 4 phenotypes is unjustified from a pathophysiological point of view. It is rather a random collection of clinical characteristics with many of those having a variable degree of life-threatening significance. In contrast to the preceding classification, a robust clinical phenotype should have characteristics that could easily identify an entity with well-defined pathophysiology. The classification of the clinical forms of HF in discrete categories (phenotypes) should recognize the basic disease process in order to apply the appropriate treatment. In general, the definition of a cluster suggests that there is an internal "togetherness" of the different clinical characteristics, but the definition does not imply that 2 particular characteristics in the same cluster obligatorily have much in common (3). In reality, the mentioned cardiac symptoms, signs, and biological elements are nodes with some associative memory in a vast network of clinical connections, but they do not form a genuine phenotype with discrete pathophysiology.

To explain the molecular, physiological, and pathological alterations of HF, we should shift attention to the integrated methodology of systems biology approach. The nature of the HF syndrome is characterized by a progressive clinical deterioration that is explained better with further integration of data from the fields of modeling, "omics," and complex networks. A new conceptual paradigm of HF progression needs the construction of novel models (phenotypes) and clinical networks (clusters) that include the characteristic emergent properties (signs, symptoms, and biological markers) of the HF syndrome (4). The human HF syndrome is a complex entity of mechanistic nature that is interrelated with 2 adaptive functional regulatory systems, the remodeling left ventricular procedure and the homeostatic neurohumoral systems. The activation of the self-organized positive feedback stabilization mechanisms of the renin-angiotensin-aldosterone system, the adrenergic system, and the natriuretic peptide axis system are important to strengthen or suppress the cardiac remodeling procedure.

Francis et al. (5), in an editorial comment regarding the paper of Ahmad et al. (1), stress the importance of "pairing phenotypes identified with cluster analyses with an 'omics' approach." This is correct, but for clinical and therapeutic reasons it seems more important for there to be a meaningful physiological relationship between the various components of "clusters." With a systems biology approach, the pathophysiological "interconnection" of the